

I Claim:

1. A method for treating a pulmonary disease state in mammals by altering indigenous *in vivo* levels of nitric oxide in mammalian cells comprising contacting the mammalian cells with a therapeutically effective amount of a nitric oxide mediator, wherein the nitric oxide mediator is selected from the group consisting of pyruvates, pyruvate precursors,  $\alpha$ -keto acids having four or more carbon atoms, precursors of  $\alpha$ -keto acids having four or more carbon atoms, and the salts thereof.

2. The method according to claim 1, wherein the pyruvates are selected from the group consisting of pyruvic acid, lithium pyruvate, sodium pyruvate, potassium pyruvate, magnesium pyruvate, calcium pyruvate, zinc pyruvate, manganese pyruvate, and mixtures thereof.

3. The method according to claim 1, wherein the pyruvate precursors are selected from the group consisting of pyruvyl-glycine, pyruvyl-alanine, pyruvyl-leucine, pyruvyl-valine, pyruvyl-isoleucine, pyruvyl-phenylalanine, pyruvamide, salts of pyruvic acid, and mixtures thereof.

4. The method according to claim 1, wherein the  $\alpha$ -keto acids having four or more carbon atoms are selected from the group consisting of oxaloacetic acid, keto-glutaric acid, keto-butyric acid, keto-adipic acid, keto-caproic acid, keto-isovaleric acid, their salts and mixtures thereof.

5. The method according to claim 1, wherein the precursors of  $\alpha$ -keto acids having four or more carbon atoms are selected from the group consisting of  $\alpha$ -keto acid-glycine,  $\alpha$ -keto acid-cystine,  $\alpha$ -keto acid-alanine,  $\alpha$ -keto acid-leucine,  $\alpha$ -keto acid-valine,  $\alpha$ -keto acid-isoleucine,  $\alpha$ -keto acid-phenylalanine,  $\alpha$ -keto amide, their salts and mixtures thereof.

6. The method according to claim 1, wherein the disease state is selected from the group consisting of bacterial infections, fungal infections, viral infections, and tumors.

7. The method according to claim 6, wherein the disease state is a tumor selected from the group consisting of epidermoid carcinomas, small cell carcinomas, adenocarcinomas, and large cell carcinomas.

8. The method according to claim 6, wherein the disease state is selected from the group consisting of bacterial infections, fungal infections, and viral infections.

5           9. The method according to claim 1, wherein the levels of nitric oxide in the mammalian cells are abnormally low in the disease state.

10           10. The method according to claim 1, wherein the levels of nitric oxide in the mammalian cells are abnormally high in the disease state.

11. The method according to claim 1, wherein the nitric oxide mediator is present in an amount from about 0.1 millimoles to about 5 millimoles.

15           12. The method according to claim 11, wherein the nitric oxide mediator is present in an amount from about 0.2 millimoles to about 4.0 millimoles.

20           13. The method according to claim 1, further comprising contacting the mammalian cells with a nitric oxide source selected from the group consisting of nitric oxide, nitric oxide precursors, nitric oxide stimulators, nitric oxide donors, and nitric oxide analogs.

14. The method according to claim 13, wherein the nitric oxide source is nitric oxide.

25           15. The method according to claim 13, wherein the nitric oxide source is selected from the group consisting of L-arginine, ADP, arachidonic acid, nitroglycerin, nitroprusside, Sin-1 and SNAP.

30           16. The method according to claim 13, wherein the disease state is selected from the group consisting of bronchial asthma, acute bronchitis, emphysema, chronic obstructive emphysema, centrilobular emphysema, panacinar emphysema, chronic obstructive bronchitis, reactive airway disease, cystic fibrosis, bronchiectasis, acquired bronchiectasis, kartaagener's syndrone, acelectasis, acute atelectasis, chronic acelectasis, pneumonia, essential thrombocytemia, legionnaire's  
35           disease, psittacosis, fibrogenic dust disease, diseases due to organic dust, diseases due to irritant gases and chemicals, hypersensitivity diseases of the lung, idiopathic infiltrative diseases of the lungs, chronic obstructive pulmonary disorder, and adult respiratory distress syndrome.

17. The method according to claim 16, wherein the disease state is emphysema or asthma.

18. The method according to claim 13, wherein the nitric oxide source is present in an amount from about 10ppm to about 50ppm.

19. The method according to claim 18, wherein the nitric oxide source is present in an amount from about 15ppm to about 45ppm.

20. The method according to claim 13, wherein the nitric oxide mediator is administered prior to administration of the nitric oxide source.

21. The method according to claim 13, wherein the nitric oxide mediator is administered concomitantly with administration of the nitric oxide source.

22. The method according to claim 13, wherein the nitric oxide mediator is administered after administration of the nitric oxide mediator.

23. The method according to claim 1, further comprising contacting the mammalian cells with a therapeutic agent.

24. The method according to claim 23, wherein the therapeutic agent is selected from the group consisting of antibacterials, antivirals, antifungals, antitumors, antihistamines, proteins, enzymes, hormones, nonsteroidal anti-inflammatories, cytokines, and steroids.

25. The method according to claim 23, wherein the therapeutic agent is administered prior to administration of the nitric oxide mediator.

26. The method according to claim 23, wherein the therapeutic agent is administered concomitantly with administration of the nitric oxide mediator.

27. The method according to claim 23, wherein the therapeutic agent is administered after administration of the nitric oxide mediator,

28. The method according to claim 1, further comprising contacting the mammalian cells with a therapeutic agent and a nitric oxide source selected from the group consisting of nitric oxide, nitric oxide precursors, and nitric oxide stimulators.

29. The method according to claim 1, wherein the nitric oxide mediator is inhaled.

5           30. A method for treating a pulmonary disease state in mammals by protecting indigenous *in vivo* levels of nitric oxide in mammalian cells during ozone inhalation comprising contacting the mammalian cells with a therapeutically effective amount of a nitric oxide mediator, wherein the nitric oxide mediator is selected from the group consisting of pyruvates, pyruvate precursors,  $\alpha$ -keto acids  
10           having four or more carbon atoms, precursors of  $\alpha$ -keto acids having four or more carbon atoms, and the salts thereof.

          31. The method according to claim 30, wherein the pyruvates are selected from the group consisting of pyruvic acid, lithium pyruvate, sodium pyruvate,  
15           potassium pyruvate, magnesium pyruvate, calcium pyruvate, zinc pyruvate, manganese pyruvate, and mixtures thereof.

          32. The method according to claim 30, wherein the pyruvate precursors are selected from the group consisting of pyruvyl-glycine, pyruvyl-alanine,  
20           pyruvyl-leucine, pyruvyl-valine, pyruvyl-isoleucine, pyruvyl-phenylalanine, pyruvamide, salts of pyruvic acid, and mixtures thereof.

          33. The method according to claim 30, wherein the  $\alpha$ -keto acids having four or more carbon atoms are selected from the group consisting of oxaloacetic acid, keto-glutaric acid, keto-butyric acid, keto-adipic acid, keto-caproic acid, keto-  
25           isovaleric acid, their salts and mixtures thereof.

          34. The method according to claim 30, wherein the precursors of  $\alpha$ -keto acids having four or more carbon atoms are selected from the group consisting of  
30            $\alpha$ -keto acid-glycine,  $\alpha$ -keto acid-cystine,  $\alpha$ -keto acid-alanine,  $\alpha$ -keto acid-leucine,  $\alpha$ -keto acid-valine,  $\alpha$ -keto acid-isoleucine,  $\alpha$ -keto acid-phenylalanine,  $\alpha$ -keto amide, their salts and mixtures thereof.

          35. The method according to claim 30, wherein the disease state is selected from the group consisting of primary pulmonary hypertension,  
35           chronic obstructive pulmonary disease, adult respiratory distress syndrome, congenital heart disease, cystic fibrosis, sarcoidosis, cor pulmonale, pulmonary embolism, bronchiectasis, emphysema, Pickwickian

syndrome, sleep apnea, congestive heart failure, and valvular heart disease.

36. The method according to claim 30, wherein the nitric oxide mediator  
5 is present in an amount from about 0.1 millimoles to about 5 millimoles.

37. The method according to claim 36, wherein the nitric oxide mediator  
is present in an amount from about 0.2 millimoles to about 4.0 millimoles.

10 38. The method according to claim 30, further comprising contacting the  
mammalian cells with a nitric oxide source selected from the group consisting of  
nitric oxide, nitric oxide precursors, nitric oxide stimulators, nitric oxide donors,  
and nitric oxide analogs.

15 39. The method according to claim 38, wherein the nitric oxide source is  
nitric oxide.

20 40. The method according to claim 38, wherein the nitric oxide source is  
selected from the group consisting of L-arginine, ADP, arachidonic acid,  
nitroglycerin, nitroprusside, Sin-1 and SNAP.

41. The method according to claim 38, wherein the nitric oxide source is  
present in an amount from about 10ppm to about 50ppm.

25 42. The method according to claim 41, wherein the nitric oxide source is  
present in an amount from about 15ppm to about 45ppm.

43. The method according to claim 38, wherein the nitric oxide mediator  
is administered prior to administration of the nitric oxide source.

30 44. The method according to claim 38, wherein the nitric oxide mediator  
is administered concomitantly with administration of the nitric oxide source.

35 45. The method according to claim 38, wherein the nitric oxide mediator  
is administered after administration of the nitric oxide mediator.

46. The method according to claim 30, further comprising contacting the  
mammalian cells with a therapeutic agent.

47. The method according to claim 46, wherein the therapeutic agent is selected from the group consisting of antibacterials, antivirals, antifungals, antitumors, antihistamines, proteins, enzymes, hormones, nonsteroidal anti-inflammatories, cytokines, and steroids.

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48. The method according to claim 46, wherein the therapeutic agent is administered prior to administration of the nitric oxide mediator.

49. The method according to claim 46, wherein the therapeutic agent is administered concomitantly with administration of the nitric oxide mediator.

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50. The method according to claim 46, wherein the therapeutic agent is administered after administration of the nitric oxide mediator,

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51. The method according to claim 30, wherein the nitric oxide mediator is inhaled.